



King's Research Portal

DOI:

[10.1016/j.jamda.2016.05.006](https://doi.org/10.1016/j.jamda.2016.05.006)

Document Version

Peer reviewed version

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Sandvik, R. K., Selbaek, G., Bergh, S., Aarsland, D., & Husebo, B. S. (2016). Signs of Imminent Dying and Change in Symptom Intensity During Pharmacological Treatment in Dying Nursing Home Patients: A Prospective Trajectory Study. *Journal Of The American Medical Directors Association*, 17(9), 821-827. <https://doi.org/10.1016/j.jamda.2016.05.006>

Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.



JAMDA

journal homepage: www.jamda.com

Original Study

Signs of Imminent Dying and Change in Symptom Intensity During Pharmacological Treatment in Dying Nursing Home Patients: A Prospective Trajectory Study

Reidun K. Sandvik MSc^{a,b,c,*}, Geir Selbaek PhD^{a,d,e}, Sverre Bergh PhD^a,
Dag Aarsland PhD^{f,g}, Bettina S. Husebo PhD^{b,h}

^a Centre for Old Age Psychiatric Research, Innlandet Hospital Trust, Ottestad, Norway

^b Department of Global Public Health and Primary Care, Centre for Elderly and Nursing Home Medicine, University of Bergen, Bergen, Norway

^c Institute for Nursing Subjects, Bergen University College, Bergen, Norway

^d Norwegian National Advisory Unit on Ageing and Health, Vestfold Hospital Trust, Tonsberg, Norway

^e Faculty of Medicine, University of Oslo, Oslo, Norway

^f Department of Old Age Psychiatry, Institute of Psychiatry, Psychology & Neuroscience King's College, London, UK

^g Center for Age-Related Medicine, Stavanger University Hospital, Stavanger, Norway

^h Municipality of Bergen, Bergen, Norway

Keywords:

Imminent dying
palliative care
end-of-life care
symptom management
dementia
nursing home medicine

ABSTRACT

Objectives: To investigate whether it is possible to determine signs of imminent dying and change in pain and symptom intensity during pharmacological treatment in nursing home patients, from day perceived as dying and to day of death.

Design: Prospective, longitudinal trajectory trial.

Setting: Forty-seven nursing homes within 35 municipalities of Norway.

Participants: A total of 691 nursing home patients were followed during the first year after admission and 152 were assessed carefully in their last days of life.

Measurements: Time between admission and day of death, and symptom severity by Edmonton symptom assessment system (ESAS), pain (mobilization-observation-behavior-intensity-dementia-2), level of dementia (clinical dementia rating scale), physical function (Karnofsky performance scale), and activities of daily living (physical self-maintenance scale).

Results: Twenty-five percent died during the first year after admission. Increased fatigue (logistic regression, odds ratio [OR] 1.8, $P = .009$) and poor appetite (OR 1.2, $P = .005$) were significantly associated with being able to identify the day a person was imminently dying, which was possible in 61% of the dying ($n = 82$). On that day, the administration of opioids, midazolam, and anticholinergics increased significantly ($P < .001$), and was associated with amelioration of symptoms, such as pain (mixed-models linear regression, 60% vs 46%, $P < .001$), anxiety (44% vs 31%, $P < .001$), and depression (33% vs 15%, $P < .001$). However, most symptoms were still prevalent at day of death, and moderate to severe dyspnea and death rattle increased from 44% to 53% ($P = .040$) and 8% to 19% ($P < .001$), respectively. Respiratory symptoms were not associated with opioids or anticholinergics.

Conclusion: Pharmacological treatment ameliorated distressing symptoms in dying nursing home patients; however, most symptoms, including pain and dyspnea, were still common at day of death. Results emphasize critical needs for better implementation of guidelines and staff education.

Trial registration: ClinicalTrials.gov NCT01920100.

© 2016 AMDA – The Society for Post-Acute and Long-Term Care Medicine. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

The authors declare no conflicts of interest.

* Address correspondence to Reidun K. Sandvik, MSc, Department of Global Public Health and Primary Care, University of Bergen, Kalfarveien 31, Bergen N-5020, Norway.

E-mail address: Reidun.Sandvik@igs.uib.no (R.K. Sandvik).

<http://dx.doi.org/10.1016/j.jamda.2016.05.006>

1525-8610/© 2016 AMDA – The Society for Post-Acute and Long-Term Care Medicine. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

The rapidly aging population, combined with substantial urban changes in the society, makes the role of institutional care increasingly important for the dying old. Every year, approximately 20% of all dying UK citizens¹ and almost 50% of the dying Norwegian population, die in a nursing home.²

More than 80% of all nursing home patients have dementia, a chronic, usually progressive and incurable disease, with increased risk of neuropsychiatric symptoms and mortality.^{3,4} To enhance advance care planning and end-of-life care in nursing homes, mid- and short-term prognostication⁵ and pain and symptom management are key responsibilities for the clinician.^{6,7} According to the newest National Institute for Health and Care Excellence (NICE) guidelines, *Care of dying adults in the last days of life*, the recognition and weighing up of factors that may indicate that someone is imminently dying are complex and underestimated.⁸ Challenges are even more urgent in nursing home patients and people with dementia.⁹ Mitchell et al¹⁰ demonstrated that pneumonia, repeated episodes of fever, and eating problems increased the 6-month mortality risk in people with dementia. In the last 3 months of life, dyspnea, pain, and pressure ulcers were identified to be the most common and distressing symptoms in these individuals. However, many nursing home patients die unexpectedly and suddenly because signs and symptoms for prognostication of the imminent death are not yet established, leading to increased

suffering of the individual.¹¹ A Dutch observational study reported that identifying a patient as terminally ill was possible only when the person died within the next 3 days.¹² Patients in this study were recognized as imminent dying by the lack of fluid and nutrition intake, general weakness, dyspnea, and somnolence. Another nursing home study found significant decrease of pain and distressing symptoms during the last 2 days of life, by retrospective observation.¹³ Contrary to these findings, pain, agitation, and dyspnea were found in 6% to 71% of affected patients, in the last week and days before death.¹⁴

Better predictability and treatment of these symptoms may contribute to the overall end-of-life care in nursing homes, and most recent recommendations emphasized the importance of prospective studies in elderly patients and people with dementia.¹⁵ Few studies have, however, assessed prospectively the change of pain and symptom intensity alongside pharmacological treatment, from the day when the patient was imminently dying and to the day of death.

We identified, prospectively, typical signs and symptoms prevalent on the day when the patient was imminently dying and the day of

Table 1
Measurement Tools Used in the Study

	What Does the Tool Measure?	Tool Characteristics and Psychometric Properties	Time Point for Measurement
ESAS	Pain and distressing symptoms (fatigue, drowsiness, nausea, appetite disturbances, dyspnea, depression, anxiety, and well-being)	Edmonton symptom assessment system (ESAS) evaluates subitem intensity on an 11-point Likert scale (range 0–10). Intensity is grouped as none to mild (0–2), mild to moderate (3–6), and moderate to severe (7–10). ³⁷ ESAS has shown good psychometric properties, and has been used in dying people with dementia. ^{15–17}	Baseline
ESAS	Pain and distressing symptoms (fatigue, drowsiness, nausea, appetite disturbances, dyspnea, depression, anxiety, sleep, vomiting, delirium, agitation, death rattle, and constipation)	ESAS evaluates subitem intensity on an 11-point Likert scale (range 0–10). Intensity is grouped as none to mild (0–2), mild to moderate (3–6), and moderate to severe (7–10). ³⁷ ESAS has shown good psychometric properties, and has been used in dying people with dementia. ^{15–17}	Day perceived as dying, day of death
CDR	Cognitive staging tool	Clinical dementia rating (CDR) consists of 5 steps (0–3) distributed as follows: no dementia (0 and 0.5), mild dementia (1), moderate dementia (2), severe dementia (3). CDR is a reliable, valid, and feasible tool, validated in the Norwegian language. ²⁷	Baseline
KPS	Functional performance status	Karnofsky performance status scale (KPS) is an 11-step rating scale from normal function (100), to dead (0). KPS demonstrates good psychometric properties in patients with cancer and in elderly people. ²¹	Baseline, day perceived as dying
MMSE	Cognitive staging tool with 8 domains (orientation to time and place, short-term recall, attention, and calculation, long-term recall, language, repetition, and complex commands)	Mini-mental state examination (MMSE) is a 30-point questionnaire (0–30); severe impairment (0–11), moderate impairment (12–17), mild impairment (18–23), and no impairment (24–30). MMSE is widely used and demonstrates good validity and reliability. ^{23–26}	Baseline
MOBID-2	Pain intensity and pain location from musculoskeletal pain (Part 1), and pain from internal organs, head, and skin (Part 2)	Mobilization-observation-behavior-intensity-dementia-2 Pain Scale (MOBID-2) assesses pain intensity and pain location based on patient's pain behavior during standardized, guided movements. The 10 items are scored on a 0–10 numerical rating scale (0 = no pain, 10 = severe pain). Based on all observations, the patient's overall pain intensity is rated again on a 0–10 scale. MOBID-2 has excellent reliability, validity, and good responsiveness. ¹⁸	Baseline, day perceived as dying, day of death
PSMS	Activities of daily living are assessed by 6 domains (toileting, eating, dressing, grooming, transfer, and bathing)	Lawton and Brody physical self-maintenance scale (PSMS) has 6 domains, each scored on a scale from 1–5 (range 6–30). Increasing numbers means increasing dependence in daily functioning. Good reliability and validity, and sensitive to change in severe dementia. ^{19,20}	Baseline
RAI-PC	Distressing symptoms, care and treatment provided	Residents Assessment Instrument for Palliative Care (RAI-PC) consists of 8 domains (symptoms, communication, mood, functional status, preferences, social relations, spirituality, and treatments), of which we included items for mouth care, bedsores, and nutrition. ²²	Baseline, day perceived as dying, day of death

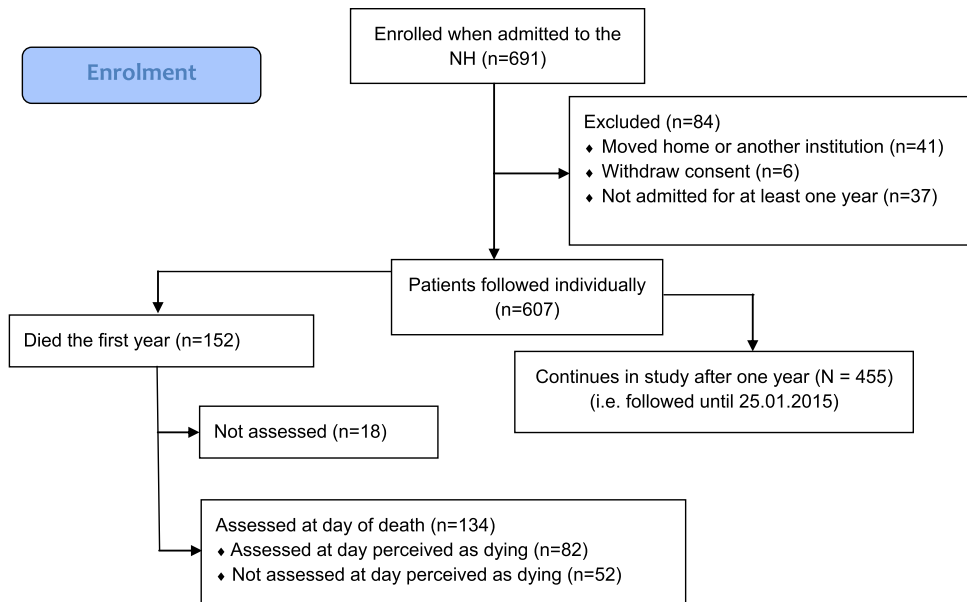


Fig. 1. Study flow chart for 691 patients individually admitted to 47 Norwegian nursing homes (NH) from January 2012 to June 2014.

death. Further, we investigated whether opioids, anxiolytics, and anticholinergics were associated with change of pain and symptom intensity between these 2 time points.

Methods

This was a prospective, multicenter longitudinal trajectory study including 47 nursing homes from 35 municipalities, in 4 counties of Norway. Between January 2012 and June 2014, eligible participants, aged 65 years and older or younger people with an early diagnosis of dementia, were included. They were all admitted to long-term care units and had an expected survival of 6 months or more as judged by the multidisciplinary team (responsible nursing home physician, the responsible nurse, and the primary caregiver). Data were collected for each patient individually, at admission to the nursing home (baseline), at the day the person was perceived as dying (imminent dying), and at the day of death. In our analyses, we included only patients followed for at least 1 year until January 1, 2015, or until death.

Registered nurses and licensed practical nurses (usually the primary caregiver) with close knowledge of the patient performed all assessments under supervision by experienced research nurses. When a patient was not able to give valid self-report due to dementia or unconsciousness, the primary caregiver performed as a proxy-rater. The assessors participated in a 2-day standardized training program (12 hours) and received specific training in use of the instruments, before the data collection. End-of-life care was performed according to standard procedures at each individual nursing home. When a patient showed deteriorating health conditions, the multidisciplinary team evaluated whether the individual was imminently dying by clinical signs due to their own clinical experience. On this day and at the day of death, data were compiled in a telephone interview between the patient's primary caregiver and the research nurse, including standardized measurement scales (Table 1).

Pain and distressing symptoms were assessed at baseline (T0), the day a patient was imminently dying (T1), and the day of death (T2), using the Edmonton symptom assessment system (ESAS) with symptoms of fatigue, drowsiness, nausea, poor appetite, dyspnea, depression, anxiety, and well-being.¹⁶ Six additional symptoms (sleep disturbances, vomiting, delirium, agitation, death rattle, and constipation) were also assessed at T1 and T2 (Table 1). Moderate and

severe symptoms on the ESAS scores (score ≥ 3) were regarded as clinically significant.¹⁷ The scale has been used and validated for proxy-rating,¹⁸ but has not yet been used in dying patients with dementia. We

Table 2

Baseline Clinical Characteristics for Patients Admitted Individually to a Nursing Home From January 2012 to June 2014

Characteristics	Total Sample, n = 607	Dying Within 1 Year, n = 152	Alive ≥ 1 Year, n = 455	P*
Age, y, mean (SD)	86.3 (7.5)	86.4 (6.9)	86.3 (7.7)	.944
Female, n (%)	388 (63.9)	90 (59.2)	298 (65.5)	.162
KPS (0–100), mean (SD)	54.3 (28.8)	53.9 (53.9)	54.4 (14.0)	.882
MMSE (0–30), mean (SD)	16.2 (6.5)	15.7 (7.0)	16.3 (6.4)	.549
CDR (0, 0.5), n (%)	78 (13.3)	23 (16)	55 (12.4)	.006
CDR (1), n (%)	142 (24.1)	33 (22.9)	109 (24.5)	
CDR (2), n (%)	247 (41.9)	47 (32.6)	200 (44.9)	
CDR (3), n (%)	122 (20.7)	41 (28.5)	81 (18.2)	
PSMS (6–30), mean (SD)	15.4 (0.2)	17.3 (4.8)	14.8 (4.3)	<.001
MOBID-2 (0–10), mean (SD)	2.1 (0.1)	2.3 (2.3)	2.0 (2.1)	.199
ESAS symptoms, mean (SD)				
Pain, mean (SD)	2.6 (2.6)	3.1 (2.6)	2.5 (2.5)	.044
Fatigue, mean (SD)	2.9 (2.7)	3.6 (3.1)	2.7 (2.6)	.001
Drowsiness, mean (SD)	2.7 (2.7)	3.6 (2.9)	2.5 (2.5)	.001
Nausea, mean (SD)	0.6 (1.6)	0.8 (1.9)	0.6 (1.5)	.211
Poor appetite, mean (SD)	1.4 (2.5)	2.0 (3.0)	1.2 (2.3)	.003
Dyspnea, mean (SD)	1.3 (2.2)	2.0 (2.8)	1.0 (2.0)	<.001
Depression, mean (SD)	2.4 (2.6)	2.4 (1.9)	2.3 (2.6)	.771
Anxiety, mean (SD)	2.2 (2.8)	2.6 (3.2)	2.1 (2.7)	.088
Well-being, mean (SD)	3.0 (2.5)	3.5 (2.7)	2.9 (2.4)	.019
RAI-PC items, n (%)				
Problems chewing	26 (7.2)	11 (12.1)	15 (5.6)	.037
Problems swallowing	28 (7.8)	12 (13.2)	16 (5.9)	.025
Mouth pain	11 (3.1)	7 (7.7)	4 (1.5)	.003
Nutritional problems	57 (15.8)	19 (20.9)	38 (14.1)	.127
Nutritional substitute	55 (15.3)	22 (24.2)	33 (12.3)	.006
Bedsore, stage 1	41 (12.4)	17 (20.7)	24 (9.6)	.008
Bedsore, stage 2	52 (15.9)	24 (29.6)	28 (11.4)	<.001
Bedsore, stage 3	14 (4.4)	7 (9.3)	7 (2.9)	.017
Bedsore, stage 4	5 (1.6)	1 (1.3)	4 (1.7)	.846

CDR, higher score indicates higher cognitive impairment; ESAS, higher scores indicate more severe symptoms; KPS, lower scores indicate more dependence; MMSE, lower scores indicate more cognitive impairment; PSMS, increasing numbers indicate higher dependency.

*P value from exact χ^2 test for dichotomous variables and otherwise *t* test comparing those who died within 1 year with those who were alive after 1 year.

also investigated pain (T0, T1, T2) (scores on mobilization-observation-behavior-intensity-dementia-2 [MOBID-2]),¹⁹ activities of daily living (physical self-maintenance scale [PSMS]),^{20,21} and physical function by the Karnofsky performance scale (KPS).²² We further included the items for nutrition, bedsores, and mouth care assessed by the resident assessment instrument for palliative care (RAI-PC).²³ Cognition and level of dementia were assessed by mini-mental state examination (MMSE)^{24–27} and clinical dementia rating scale (CDR) at T0.²⁸ Administered pharmacological treatment and the causes of death were collected from the patients' medical records.

At nursing home admission, verbal and written informed consent was obtained in direct conversations with all cognitively intact patients with sufficient ability to consent. In patients lacking the ability to consent, verbal and written informed and presumed consent was obtained in direct conversation with the patient (if possible) and his or her legal guardian, usually a family member, after explaining the aims and protocol of the study. The study was approved by the Regional Committee for Medical and Health Research Ethics 2011/1738, and registered at clinicaltrials.gov NCT01920100.

Continuous variables were described by means and SDs, and categorical variables by percentages of sample size and χ^2 square test. The change within individuals in continuous variables was analyzed with the paired *t* test. To examine differences between groups and time points, we also built regression models for repeated measurements with random effects for intercepts: linear mixed model for continuous and multilevel logistic regression for dichotomous outcome variables. We regarded $P < .050$ as significant and $P < .001$ as highly significant. Statistical analyses were conducted with IBM SPSS Statistics for Windows version 21.0 (IBM Corp, Armonk, NY), and STATA/IC 13.1 (Stata Corp, College Station, TX).

Results

In all, 691 patients from 47 Norwegian nursing homes were included for the baseline assessment (T0). Forty-seven patients were excluded from further follow-up testing because they moved home or to other institutions or declined to participate (Figure 1). To avoid noninformative censoring, we also excluded 37 patients with nursing home stay less than 1 year. This left 607 patients for the follow-up analyses, of whom 369 (63%) had moderate to severe dementia according to the CDR scale (Table 2). A total of 152 patients (25%) died during the first year; of those, 18 were excluded from our analyses because of missing data (Figure 1). The remaining 134 patients were all assessed on their day of death (T2). For 82 patients (61%), the multidisciplinary team identified the day of imminent dying (T1), whereas 52 patients were not recognized as dying, in advance. Thus, our analyses comprised 82 patients at T1 and 134 at T2. The median number of days between T1 and T2 was 2 (range 0–73); 63% died between day 0 and 2, 21% died between days 3 and 7, and 15% died on day 8 or more.

Predictors for 1-Year Mortality

Patients ($n = 152$, 25%) who died during the first year had more dyspnea ($P < .001$), drowsiness ($P = .001$), fatigue ($P = .001$), pain ($P = .044$), and dependency in daily activities ($P < .001$) at admission (T0), and experienced less well-being ($P = .019$) and appetite ($P = .003$), compared with those who were still alive after 1 year ($n = 455$) (Table 2). These patients had also more chewing and swallowing problems ($P = .037$, $P = .025$, respectively), pain in the mouth ($P = .003$), nutritional substitution ($P = .006$), and bedsores stage 1, 2, and 3 ($P = .008$, $P < .001$, and $P = .017$, respectively). Diagnoses of death suggested that 21% died of pneumonia, followed by heart failure (18%), dementia (15%), stroke (15%), and cancer (7%) or

kidney failure (7%). In 17% of the patients, diagnoses of death were missing for administrative reasons.

Signs and Symptoms of Imminent Dying (T1)

Shown in Table 3, fatigue (99%), drowsiness (98%), and reduced appetite (95%) were the most frequently observed ESAS symptoms with moderate to severe intensity at T1. Moderate to severe pain assessed with ESAS was found in 60% of the patients, highly correlated

Table 3
Proportion of Patients (%) Categorized According to Severity of ESAS Symptoms in Nursing Home Patients at Day of Imminently Dying and Day of Death

Symptoms	Day of Imminently Dying, n = 82		Day of Death, n = 134		P*
	%	95% CI	%	95% CI	
Pain, 0–10					<.001
0–2	39.7	(29.3–51.2)	54.2	(45.1–63.0)	
3–6	34.6	(24.7–46.0)	32.5	(24.6–41.5)	
7–10	25.6	(17.0–36.7)	13.3	(8.3–20.8)	
Fatigue, 0–10					.001
0–2	1.3	(0.0–0.9)	10.6	(6.2–17.5)	
3–6	17.9	(10.8–28.3)	10.5	(6.2–17.5)	
7–10	80.8	(70.3–88.2)	78.9	(70.6–85.3)	
Drowsiness, 0–10					<.001
0–2	2.5	(0.6–1.0)	12.2	(7.4–19.3)	
3–6	19.2	(11.8–29.7)	11.4	(6.8–18.4)	
7–10	78.2	(67.4–86.1)	76.4	(68.0–83.2)	
Sleep quality, 0–10					<.001
0–2	50	(38.7–61.3)	61.2	(51.4–70.3)	
3–6	31.6	(22.0–43.1)	19.1	(12.9–27.5)	
7–10	18.4	(11.1–29.0)	19.1	(12.9–27.5)	
Nausea, 0–10					<.001
0–2	75.6	(64.7–84.0)	87.7	(80.5–92.3)	
3–6	19.2	(11.8–29.7)	6.6	(3.2–12.7)	
7–10	5.1	(1.9–13.1)	5.7	(2.7–11.7)	
Vomiting, 0–10					<.001
0–2	84.6	(74.6–91.2)	90.2	(83.5–94.4)	
3–6	10.2	(5.1–19.4)	5.7	(2.7–11.6)	
7–10	5.1	(1.9–13.1)	4.1	(1.7–9.5)	
Poor appetite, 0–10					<.001
0–2	5.2	(1.9–13.3)	21.7	(15.4–30.3)	
3–6	6.5	(2.7–14.9)	9.6	(5.3–16.6)	
7–10	88.3	(78.8–93.9)	68.7	(59.5–76.6)	
Dyspnea, 0–10					.040
0–2	56.6	(45.0–67.5)	47.1	(38.3–56.1)	
3–6	22.4	(14.2–33.4)	24.0	(17.1–32.5)	
7–10	21.1	(13.2–31.9)	29.0	(21.5–38.0)	
Depression, 0–10					<.001
0–2	66.7	(55.0–76.6)	84.9	(77.1–90.3)	
3–6	16.0	(9.2–26.4)	8.4	(4.5–15.0)	
7–10	17.3	(10.2–27.9)	6.7	(3.3–13.0)	
Anxiety, 0–10					<.001
0–2	55.8	(44.4–66.7)	69.1	(60.3–76.7)	
3–6	24.7	(16.2–35.8)	15.4	(10.0–23.1)	
7–10	19.5	(12.0–30.1)	15.4	(10.0–23.1)	
Delirium, 0–10					<.001
0–2	84.0	(73.6–90.8)	91.1	(84.4–95.0)	
3–6	8.0	(3.6–16.9)	2.4	(3.3–12.6)	
7–10	8.0	(3.6–17.0)	0.7	(0.1–0.7)	
Agitation, 0–10					<.001
0–2	90.8	(81.6–95.6)	96.7	(91.5–98.8)	
3–6	6.6	(2.7–15.1)	2.4	(0.1–0.7)	
7–10	2.6	(0.6–10.2)	0.8	(0.1–5.7)	
Death rattle, 0–10					<.001
0–2	92.3	(83.7–96.6)	81.5	(73.5–87.4)	
3–6	5.1	(1.8–13.1)	10.4	(6.1–17.3)	
7–10	2.6	(0.6–10.0)	8.1	(4.4–14.5)	
Constipation, 0–10					<.001
0–2	75.6	(64.7–84.0)	91.8	(85.3–95.6)	
3–6	20.5	(12.8–31.2)	7.3	(3.8–13.7)	
7–10	3.5	(1.2–11.5)	0.8	(0.1–5.7)	

*Mixed-models linear regression symptom as dependent variable and time as independent variable

Table 4

Proportion of Patients (%) by Administered Analgesic Drugs at Day of Imminently Dying and Day of Death

Drugs	Day of Imminently Dying, n = 82		Day of Death, n = 134		P*
	%	95% CI	%	95% CI	
Paracetamol	51.9	40.8–62.7	35.1	27.4–43.6	.445
Weak opioids [†]	3.7	1.2–11.1	37.3	29.5–45.9	<.001
Strong opioids [‡]	48.1	37.3–59.2	65.7	57.1–73.3	<.001
Benzodiazepines	23.5	15.3–34.1	13.4	8.6–20.4	.841
Midazolam	8.6	4.1–17.3	17.2	11.6–24.6	<.001
Antiemetics	1.2	1.2–8.5	3.0	1.1–7.8	.174
Anticholinergics [§]	6.2	2.5–14.2	18.6	12.9–26.3	<.001
Haloperidol	6.2	2.5–14.2	6.0	3.0–11.6	.255

*P value from exact χ^2 test.[†]Codeine, tramadol.[‡]Morphine, fentanyl, oxycodone, buprenorphine.[§]Glycopyrronium bromide, morphine-scopolamine, scopolamine.

with the total scores on the MOBID-2 Pain Scale (Spearman rho correlation 0.618, $P < .001$). Moderate to severe degree of sleep disturbances (50%), anxiety (44%), dyspnea (44%), and depression (33%) were also common at T1.

We entered the variable identified/not identified as imminently dying into logistic regression analyses with all ESAS symptoms at day of death. We found that increased fatigue (odds ratio [OR] 1.8, 95% confidence interval [CI] 1.16–2.85, $P = .009$) and poor appetite (OR 1.2, 95% CI 1.06–1.41, $P = .005$) were significantly associated with being able to identify the day a person was imminently dying; however, symptoms of pain or dyspnea did not contribute to the recognition of imminent dying, and the presence of delirium was associated with not being able to identify a person as dying at T1 (OR 0.6, 95%CI 0.4–0.9, $P = .010$).

Pain and Symptom Intensity at Day of Death (T2)

Moderate and severe degree of fatigue (89%), drowsiness (88%), and reduced appetite (78%) were still most frequently observed at T2 (Table 3). We found a proportional amelioration in patients with pain (60% vs 46%, $P < .001$), anxiety (44% vs 31%, $P < .001$), depression (33% vs 15%, $P < .001$), nausea (24% vs 12%, $P < .001$), constipation (24% vs 8%, $P < .001$), and delirium (16% vs 3.1%, $P < .001$) from T1 to T2. Dyspnea was frequently observed in the patients, and increased from 44% to 53% ($P = .040$). The proportion of patients with death rattle increased from 8% to 19% ($P < .001$) (Table 3). Between T1 and T2, the prevalence of agitation and delirium together decreased from 57% to 19% ($P < .001$). Patients who in advance were identified as dying ($n = 82$, 61%) showed significantly more fatigue ($P < .001$), drowsiness ($P = .006$), and loss of appetite ($P < .001$) compared with those who died unexpectedly ($n = 52$, 39%).

Pain and Symptom Management in the Last Days and Hours of Life

Paracetamol was the most frequently used drug (52%) on day of imminent dying. The administration of strong opioids increased from 48% to 66% ($P < .001$) and weak opioids increased from 4% to 37% ($P < .001$) between T1 and T2. The use of midazolam doubled from 9% to 17% ($P < .001$), whereas anxiolytics, in general, were stable with 29% at T1 and 30% at T2 ($P = .781$). Anticholinergic drug prescription increased from 6% to 19% ($P < .001$), and antiemetics decreased from 15% to 10% ($P = .008$) (Table 4). The linear mixed-models regression analyses investigated changes in ESAS symptom scores only in patients ($n = 75$) who started pharmacological treatment between T1 and T2 (Table 5). The initiation of opioids was associated with reduced pain intensity ($P = .041$), nausea ($P = .035$), death rattle ($P = .016$), and agitation ($P = .002$), but not dyspnea ($P = .350$). The use of anxiolytics/sedatives was associated with the reduction of nausea ($P = .031$), agitation ($P = .015$), death rattle ($P = .011$), and dyspnea ($P = .007$). Finally, anticholinergics were associated with reduced anxiety ($P = .012$) and agitation ($P < .001$) but not death rattle.

Discussion

This study found that 1 in 4 patients died during the first year after nursing home admission, most often with diagnoses of pneumonia, heart failure, and dementia. The day of imminent dying was identified in 61% by fatigue and poor appetite. In the last days of life, the administration of opioids, midazolam, and anticholinergics increased significantly and was associated with the amelioration of symptoms such as pain, anxiety, and depression.

This was, to our knowledge, the first study that prospectively assessed the change of pain and symptom intensity between the day of imminent dying (T1) and the day of death (T2). Alarming findings uncovered the high number of patients who still experienced dyspnea (53%), pain (46%), sleep problems (40%), and anxiety (31%) at T2. Moreover, the prevalence of death rattle increased from 8% to 19%. Compared with other studies,^{11,14} agitation and delirium were less frequently observed at the end of life. It is uncertain, however, whether amelioration of agitated symptoms was related only to the treatment of pain or increased physical weakness over time.¹¹ A possible under-detection of delirium might limit our results, as we did not include any specific tool assessing this disease by a valid delirium tool, such as the Confusion Assessment Method.²⁹ Although the administration of opioids increased from 44% to 66% between T1 and T2 in our study, figures were lower in a comparable study in which all patients (100%) received morphine (in mean 30 mg per day).¹¹ Nuanced interpretation of these results is required because the use of morphine, as a “one-size-fits-all” solution, does not necessarily guarantee good treatment. To validate the efficacy, it is a prerequisite to assess pain and symptom intensity before and after symptom management has been initiated.³⁰

Table 5

Change in ESAS Symptom Severity Between the Day of Imminently Dying and the Day of Death

Treatment Symptoms	Opioids, *n = 58			Anxiolytics/sedatives, †n = 27			Anticholinergic drugs, ‡n = 24		
	β	95% CI	P	β	95% CI	P	β	95% CI	P
Pain	−1.04	(−2.03 to −0.04)	.041	−1.00	(−2.50 to 0.54)	.206	−1.45	(−3.02 to 0.12)	.071
Nausea	−0.82	(−1.59 to 0.58)	.035	−0.92	(−1.76 to −0.08)	.031	−1.25	(−2.53 to 0.41)	.058
Death rattle	−1.05	(0.20 to 1.91)	.016	1.96	(0.45 to 3.47)	.011	1.01	(−0.05 to 2.08)	.063
Dyspnea	0.60	(−0.66 to 1 to 86)	.350	2.54	(0.71 to 4.37)	.007	0.15	(−1.74 to 2.03)	.878
Agitation	−1.13	(−1.85 to −0.41)	.002	−0.27	(−2.29 to −0.25)	.015	−2.12	(−3.23 to 0.90)	.001
Anxiety	−1.18	(−2.41 to 0.04)	.058	−0.80	(−2.90 to 1.29)	.451	−2.49	(−4.44 to 0.55)	.012

Only patients who newly started with the treatment were included in these analyses. Investigated with linear mixed-models regression analysis; ESAS subitems as dependent variables.

*Codeine, tramadol, morphine, fentanyl, oxycodone, buprenorphine.

†Benzodiazepines (including midazolam).

‡Scopolamine, morphine-scopolamine, glycopyrronium bromide.

In the present and also other studies,^{11,13,14} the most prevalent distressing symptom was dyspnea (53%), complicated by its subjective burden with multiple potential etiologies, such as pneumonia and lung edema in connection to heart failure.^{14,31} Although the exact mode of action of opioids in dyspnea management is unknown, peripheral and central mechanisms have earlier been postulated.³² Thus, it was an unexpected finding that opioids were not associated with reduction of the dyspnea intensity scores in our study. Although it is widely held that glycopyrrolate and scopolamine subcutaneously are useful treatments of death rattle in patients with cancer,³³ it may be difficult for nursing home staff to distinguish between death rattle and sounds of accumulating secretion in connection with pneumonia or heart failure with lung edema.³⁴ Diagnostic challenges also may be apparent for nausea in connection with newly started opioids in people who are no longer able to describe their suffering. Caregivers in our study observed nausea in only a very few patients; other studies did not mention this symptom.^{10,11,14}

Although it is broadly believed that the identification of imminent dying is a hallmark to initiate end-of-life care, the frequency and severity of typical symptoms have not yet been described.^{5,35} In the present study, nursing home staff identified T1 in 61% of their patients, through changes in fatigue and poor appetite. Symptoms such as pain, dyspnea, or agitation did not predict imminent death. This is noteworthy because physical symptoms of weakness do not explain the initiation of pharmacological treatment. It is possible that the diagnoses of death (pneumonia, heart failure, and dementia) are trigger factors for increased pain, dyspnea, and anxiety. Interestingly, the prevalence of pain was not associated with agitation in our study, although individual pain treatment has been demonstrated to be correlated to the reduction of pain and agitation.^{13,36–38} Compared with younger patients with cancer, the timely prognostication of death is challenging due to the patient's deterioration over a long time period.³⁵ Our findings should be used to enhance staff education in care of dying nursing home patients because these symptoms are challenging to distinguish: a prerequisite to provide proper symptom management. Although Norwegian authorities are developing a subspecialization for nursing home physicians and a master's degree for geriatric nursing, these standards are not yet established. Regular training and education of nursing home staff and medical students are priorities, but skills and competence regarding end-of-life care in people with dementia vary considerably among institutions.

Limitations and Strengths

Our study used the continuous measures of ESAS symptom scores, which to our knowledge are not validated in dying people with dementia. ESAS has previously been used in the nursing home setting and is the only end-of-life care instrument with relevant symptom list to assess change in symptom intensity during treatment by a continuous scale.^{13,39} However, the validity of proxy-rated intensity scores may always be questionable in dying patients and people with dementia. A further limitation is the lack of instruments to assess the quality of life and quality of death and dying, which is an important consideration for future studies. Additionally, to improve the situation for the dying old, we would also recommend exploring convenient nonpharmacological interventions, such as fresh air in the case of dyspnea. Beneficially, our sample size at baseline was larger than comparable studies.^{10–14} However, when we assessed the association between newly initiated pharmacological treatment and changes in pain and symptom intensity we ended up with a rather low sample of 75 people.

Conclusion

In the present study, pain and symptom management were associated with symptom relief in dying nursing home patients.

Nevertheless, too many people still experienced unacceptably high levels of pain and distressing symptoms in the last days of life, which emphasizes the critical need for user-specific guidelines, better implementation, and staff education in nursing homes.

Acknowledgment

We thank the patients, their relatives, and the nursing home staff for their willingness and motivation that made this study possible.

We also thank Geir Egil Eide, PhD, Centre for Clinical Research, Haukeland University Hospital, for statistical advice, evaluation of the results, and manuscript. BSH thanks the Norwegian Government and the GC Rieber Foundation for supporting her time for this work.

References

- Public Health England. National End of Life Care Intelligence Network Publication 2010. Available at: <http://www.endoflifecareintelligence.org.uk>. Accessed October 10, 2015.
- Folkhelseinstituttet. Statistikkbank. Secondary Statistikkbank 2015. Available at: <http://www.ssb.no>. Accessed October 10, 2015.
- Park MH, Kwon DY, Jung JM, et al. Mini-Mental Status Examination as predictors of mortality in the elderly. *Acta Psychiatr Scand* 2013;127:298–304.
- Selbaek G, Kirkevold O, Engedal K. Psychiatric and behavioural symptoms and the use of psychotropic medication in Special Care Units and Regular Units in Norwegian nursing homes. *Scand J Caring Sci* 2008;22:568–573.
- Murray SA, Kendall M, Boyd K, et al. Illness trajectories and palliative care. *BMJ* 2005;330:1007–1011.
- Flo E, Husebo BS, Bruusgaard P, et al. A review of the implementation and research strategies of advance care planning in nursing homes. *BMC Geriatr* 2016;16:24–44.
- Husebo BS, Strand LI, Moe-Nilssen R, et al. Who suffers most? Dementia and pain in nursing home patients: A cross-sectional study. *J Am Med Dir Assoc* 2008;9:427–433.
- NCCMH. Care of the dying adult. NICE clinical guideline 2015. Available at: <https://www.nice.org.uk/guidance/indevelopment/gid-cgwave0694>. Accessed December 14, 2015.
- EU Joint Programme-Neurodegenerative Disease Research. Palliative and end-of-life care research in neurodegenerative diseases 2014. Available at: <http://www.neurodegenerationresearch.eu>. Accessed October 10, 2015.
- Mitchell SL, Teno JM, Kiely DK, et al. The clinical course of advanced dementia. *N Engl J Med* 2009;361:1529–1538.
- Klapwijk MS, Caljouw MA, van Soest-Portvliet MC, et al. Symptoms and treatment when death is expected in dementia patients in long-term care facilities. *BMC Geriatr* 2014;14:99.
- Brandt HE, Deliens L, Ooms ME, et al. Symptoms, signs, problems, and diseases of terminally ill nursing home patients: A nationwide observational study in the Netherlands. *Arch Intern Med* 2005;165:314–320.
- Brandt HE, Ooms ME, Deliens L, et al. The last two days of life of nursing home patients—A nationwide study on causes of death and burdensome symptoms in the Netherlands. *Pall Med* 2006;20:533–540.
- Hendriks SA, Smalbrugge M, Galindo-Garre F, et al. From Admission to Death: Prevalence and Course of Pain, Agitation, and Shortness of Breath, and Treatment of These Symptoms in Nursing Home Residents With Dementia. *J Am Med Dir Assoc* 2015;16:475–481.
- van der Steen JT, Radbruch L, Hertogh CM, et al. White paper defining optimal palliative care in older people with dementia: A Delphi study and recommendations from the European Association for Palliative Care. *Pall Med* 2014;28:197–209.
- Chang VT, Hwang SS, Feuerman M. Validation of the Edmonton Symptom Assessment Scale. *Cancer* 2000;88:2164–2171.
- Ripamonti CI, Bandieri E, Pessi MA, et al. The Edmonton Symptom Assessment System (ESAS) as a screening tool for depression and anxiety in non-advanced patients with solid or haematological malignancies on cure or follow-up. *Support Care Cancer* 2014;22:783–793.
- Murray TM, Sachs GA, Stocking C, et al. The symptom experience of community-dwelling persons with dementia: Self and caregiver report and comparison with standardized symptom assessment measures. *Am J Geriatr Psychiatry* 2012;20:298–305.
- Husebo BS, Strand LI, Moe-Nilssen R, et al. Pain in older persons with severe dementia. Psychometric properties of the Mobilization-Observation-Behaviour-Intensity-Dementia (MOBID-2) Pain Scale in a clinical setting. *Scand J Caring Sci* 2010;24:380–391.
- Lawton MP, Brody EM. Assessment of older people: Self-maintaining and instrumental activities of daily living. *Gerontologist* 1969;9:179–186.
- Green CR, Mohs RC, Schmeidler J, et al. Functional decline in Alzheimer's disease: A longitudinal study. *J Am Geriatr Soc* 1993;41:654–661.
- Vincent M. The Karnofsky performance status scale. *Cancer* 1984;53:2002–2007.

23. Steel K, Ljunggren G, Topinkova E, et al. The RAI-PC: An assessment instrument for palliative care in all settings. *Am J Hosp Pall Care* 2003;20: 211–219.
24. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; 12:189–198.
25. Laks J, Coutinho ES, Junger W, et al. Education does not equally influence all the Mini Mental State Examination subscales and items: Inferences from a Brazilian community sample. *Rev Bras Psiquiatr* 2010;32:223–230.
26. Cullen B, Fahy S, Cunningham CJ, et al. Screening for dementia in an Irish community sample using MMSE: A comparison of norm-adjusted versus fixed cut-points. *Int J Geriatr Psychiatry* 2005;20:371–376.
27. Crum RM, Anthony JC, Bassett SS, et al. Population-based norms for the Mini-Mental State Examination by age and educational level. *JAMA* 1993;269: 2386–2391.
28. Hughes CP, Berg L, Danziger WL, et al. A new clinical scale for the staging of dementia. *Br J Psychiatry* 1982;140:566–572.
29. Inouye SK, van Dyck CH, Alessi CA, et al. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med* 1990;113:941–948.
30. Husebo BS, Ostelo R, Strand LI. The MOBID-2 pain scale: Reliability and responsiveness to pain in patients with dementia. *Eur J Pain* 2014;10: 1419–1430.
31. Hendriks SA, Smalbrugge M, Hertogh CM, et al. Dying with dementia: Symptoms, treatment, and quality of life in the last week of life. *J Pain Symptom Manage* 2014;47:710–720.
32. Del Fabbro E, Dalal S, Bruera E. Symptom control in palliative care—Part III: Dyspnea and delirium. *J Pall Med* 2006;9:422–436.
33. Rashid H, Long JD, Wadleigh RG. Management of secretions in esophageal cancer patients with glycopyrrrolate. *Ann Oncol* 1997;8:198–199.
34. Twycross R. Symptom Management in Advanced Cancer. 2nd ed. Oxon, UK: Radcliffe Medical Press; 1997.
35. Harris D. Forget me not: palliative care for people with dementia. *Postgrad Med J* 2007;83:362–366.
36. Husebo BS, Ballard C, Sandvik R, et al. Efficacy of treating pain to reduce behavioural disturbances in residents of nursing homes with dementia: cluster randomised clinical trial. *BMJ* 2011;343:d4065.
37. Husebo BS, Ballard C, Fritze F, et al. Efficacy of pain treatment on mood syndrome in patients with dementia: a randomized clinical trial. *Int J Geriatr Psychiatry* 2013;29:828–836.
38. Sandvik RK, Selbaek G, Seifert R, et al. Impact of a stepwise protocol for treating pain on pain intensity in nursing home patients with dementia: A cluster randomized trial. *Eur J Pain* 2014;18:1890–2500.
39. Selby D, Cascella A, Gardiner K, et al. A single set of numerical cutpoints to define moderate and severe symptoms for Edmonton Symptom Assessment System. *J Pain Symptom Manage* 2010;39:241–249.